DEEP INFECTIONS OF TOTAL JOINT REPLACEMENTS

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National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institute of Child Health and Human Development

THIS PA USES THE "MODULAR GRANT" AND "JUST-IN-TIME" CONCEPTS. IT INCLUDES DETAILED MODIFICATIONS TO STANDARD APPLICATION INSTRUCTIONS THAT MUST BE USED WHEN PREPARING APPLICATIONS IN RESPONSE TO THIS PA.

PURPOSE

Total joint replacement has been shown to be a highly effective treatment for end-stage arthritis of the major weight-bearing joints. Despite this success, complications persist, including dislocation, deep infection, aseptic loosening and osteolysis. Although relatively uncommon, deep infections in a total joint replacement are potentially catastrophic events for patients and for society. Through this program announcement (PA), the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) and the National Institute of Child Health and Human Development (NICHD) seek to stimulate the receipt of a broad range of basic science and clinical studies to better understand the pathophysiology, diagnosis and treatment of deep infections around total joint replacement implants. The National Institute of Allergy and Infectious Diseases (NIAID) has interests in related areas, and applications responding to this PA may receive assignment to NIAID in accordance with assignment guidelines.

HEALTHY PEOPLE 2000

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2000," a PHS led national activity for setting priority areas. This Program Announcement (PA), Deep Infections of Total Joint Replacements, is related to the priority area of chronic diseases. Potential applicants may obtain a copy of "Healthy People 2000" at http://odphp.osophs.dhhs.gov/pubs/hp2000

ELIGIBILITY REQUIREMENTS

Applications may be submitted by domestic and foreign, for-profit and non-profit organizations, public and private, such as universities, colleges, hospitals, laboratories, units of State and local governments, and eligible agencies of the Federal government. Racial/ethnic minority individuals, women, and persons with disabilities are encouraged to apply as principal investigators.

MECHANISM OF SUPPORT

This PA will use the National Institutes of Health (NIH) research project grant (R01) award mechanism. Responsibility for the planning, direction, and execution of the proposed project will be solely that of the applicant. The total project period for an application submitted in response to this PA may not exceed 5 years. Applications that are responsive to Program Announcements are candidates for discretionary funding. Additional information regarding NIAMS funding policy regarding these applications can be located at: http://www.nih.gov/niams/grants/payline2.htm

RESEARCH OBJECTIVES

Total joint replacement (TJR) is an effective salvage operation for end-stage arthritis of a diarthrodial joint. The success of these surgeries was noted by the 1994 NIH Consensus Development Conference on Total Hip Replacement. In 1996, approximately 400,000 total hip and knee replacements were performed within the United States. By 2030, it is anticipated that this number may increase to over 700,000.

Although current deep infection rates of less than 1% at 1 year post-operative are now being reported, infection of a TJR remains a devastating complication from both the patient's, and from a cost, perspective. An increased risk of infection is associated with inflammatory arthropathies, diabetes mellitus, poor nutrition, obesity, urinary tract infection, oral use of steroids, previous operation(s) on the affected joint, active concurrent infection elsewhere, debris particles, advanced age, and prolonged operative time and hospitalization.

Deep infections of prosthetic devices have the following characteristics: (1) there is a high rate of infection around a prosthetic device; (2) they are caused by pathogens that usually are of low virulence; and (3) once established, are difficult to treat. Several theories for why these deep infections around orthopaedic implants behave in this manner have been developed. In general, they look at either the interaction of the device with the bacterial pathogen, or of the device with the host.

Previous studies on the interaction of the device with bacterial pathogens showed that bacteria readily attach to devices. In addition, once attached, many encase themselves in a protective biofilm. Finally, surface attached bacteria are intrinsically more resistant to the action of white blood cells, and they may produce factors that impair the host response or cause direct tissue damage.

Previous studies investigating the interaction of the device with the host have shown that commonly used materials in TJRs (polymethylmethacrylate, stainless steel, cobalt chromium alloy, and polyethylene, all increase the host's susceptibility to infection. It has been proposed that since the host is preoccupied in responding to the device (a foreign object), attack by bacterial pathogens meets diminished resistance. It is suggested that there is a direct suppression of host defense function in device-related infections. In addition, there are reports of deficits in bactericidal activity, chemotaxis, superoxide function by polymorphonuclear leukocytes and decreased proliferation of lymphocytes in response to mitogens. Finally, the inflammatory response to the device can also result in damage to the host (i.e., IL-1B, IL-6 and TNF-alpha are all capable of producing bone resorption).

From a clinical standpoint, both the diagnosis and treatment of deep infections of TJRs remain a challenge. Only 25% of these infection can be diagnosed based upon the history and physical examination alone. Another 50% require extensive laboratory investigation with the final 25% eluding detection by commonly used diagnostic means. Once diagnosed, there is controversy surrounding what is the most effective treatment alternative. In the United States, most patients with deep infections are treated with surgical extirpation, usually in a two stage procedure (initial removal and debridement followed by a period of antibiotic treatment, then replacement of the implants). Other treatments include a one-stage procedure (removal, debridement and replacement at the same setting) or a three stage procedure (removal and debridement, insertion of a bone graft(s), and implant replacement). The latter protocols also include a course of antibiotics and may include cement (polymethylmethacrylate) mixed with antibiotics. Other concomitant treatments have been reported.

A final controversy here surrounds the use of antimicrobial prophylaxis to prevent deep infections of TJRs. Although beyond the scope of this PA, more research is necessary to identify whether late infection around prosthetic joints is caused by transient bacteremia secondary to invasive procedures, and whether antimicrobial prophylaxis can prevent them.

The following list, which is not all-inclusive, indicates potential areas for further investigation of the pathophysiology, diagnosis and treatment of deep infections of TJRs:

Define the role of non-operative treatment of these infections, including the optimum route and duration of antibiotic therapy.

Better understand the interactions between the implant device and bacterial pathogens.
Better understand the interactions between the implant device and the host.
Develop new technologies or validate current strategies for diagnosis.
-- What is the role here for diagnostic imaging (i.e. conventional imaging modalities and newer technologies such as Indium-111 polyclonal antibody scans)?
-- Is there a role for polymerase chain reaction testing of joint fluid aspirates?
Define the role of non-operative treatment of these infections, including the optimum route and duration of antibiotic therapy.
Elucidate optimal treatment strategies:
-- One versus two versus three stage revision procedures;
-- Optimal timing between removal and re-implantation;
-- Efficacy of antibiotic-impregnated bone cement;
-- Optimal ratios of antibiotics in bone cement for optimal bactericidal effect and optimal fixation;
-- Efficacy of antibiotic-loaded polymethylmethacrylate beads at the time of closure to eradicate remaining microorganisms, and a determination of optimal time period before removal;
-- Optimal time interval between bone grafting and re-implantation in a three-stage procedure;
-- Efficacy of antibiotic-impregnated spacers; and
-- Insertion of prosthesis without cement.
Determine the role of arthrodesis in treating a deep infection of a total knee replacement, including optimal timing and technique(s).
Define the optimal post-operative rehabilitation strategies following the various treatments for an infected TJR.

INCLUSION OF WOMEN AND MINORITIES IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of the NIH that women and members of minority groups and their subpopulations must be included in all NIH supported biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale and justification is provided that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43).

All investigators proposing research involving human subjects should read the "NIH Guidelines For Inclusion of Women and Minorities as Subjects in Clinical Research," which have been published in the Federal Register of March 28, 1994 (FR 59 14508-14513) and in the NIH Guide for Grants and Contracts, Vol. 23, No. 11, March 18, 1994 available on the web at the following URL address: http://grants.nih.gov/grants/guide/notice-files/not94-100.html

INCLUSION OF CHILDREN AS PARTICIPANTS IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of NIH that children (i.e., individuals under the age of 21) must be included in all human subjects research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them. This policy applies to all initial (Type 1) applications submitted for receipt dates after October 1, 1998.

All investigators proposing research involving human subjects should read the "NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects" that was published in the NIH Guide for Grants and Contracts, March 6, 1998, and is available at the following URL address: http://grants.nih.gov/grants/guide/notice-files/not98-024.html

Investigators also may obtain copies of these policies from the program staff listed under INQUIRIES. Program staff may also provide additional relevant information concerning the policy.

APPLICATION PROCEDURES

To comply with Grants policy changes beginning with the June 1, 1999 application receipt date, specific application instructions have been modified to reflect “MODULAR GRANT” and “JUST IN TIME” streamlining efforts. The modular grant concept establishes specific modules in which direct costs may be requested under this approach. The just-in-time concept allows applicants to submit certain information only when there is a possibility for an award. It is anticipated that these changes will reduce the administrative burden for the applicants, reviewers and institute/center staff. Complete and detailed instructions and information on Modular Grants can be found at http://grants.nih.gov/grants/funding/modular/modular.htm

Modular Grant applications will request direct costs in $25,000 modules, up to a total direct cost request of $250,000 per year. Applications that request more than $250,000 direct costs in any year must follow the traditional PHS398 application instructions. A typical modular grant application will request the same number of modules in each year. Application budgets will be simplified. Detailed categorical budget information will not be submitted with the application; budget form pages of the application kits will not be used. Instead, total direct costs requested for each year will be presented. Information, in narrative form, will be provided only for personnel and, when applicable, for Consortium/Contractual Costs.

The modular grant applications, total direct costs must be requested in accordance with the program guidelines and the modifications made to the standard PHS 398 application instructions described below:

PHS 398

o FACE PAGE: Items 7a and 7b should be completed, indicating Direct Costs (in $25,000 increments up to a maximum of $250,000) and Total Costs [Modular Total Direct plus Facilities and Administrative (F&A) costs] for the initial budget period Items 8a and 8b should be completed indicating the Direct and Total Costs for the entire proposed period of support.

o DETAILED BUDGET FOR THE INITIAL BUDGET PERIOD - Do not complete Form Page 4 of the PHS 398. It is not required and will not be accepted with the application.

o BUDGET FOR THE ENTIRE PROPOSED PERIOD OF SUPPORT - Do not complete the categorical budget table on Form Page 5 of the PHS 398. It is not required and will not be accepted with the application.

o NARRATIVE BUDGET JUSTIFICATION - Prepare a Modular Grant Budget Narrative page. (See http://grants.nih.gov/grants/funding/modular/modular.htm for sample pages.) At the top of the page, enter the total direct costs requested for each year. This is not a Form page.

o Under Personnel, List key project personnel, including their names, percent of effort, and roles on the project. No individual salary information should be provided. However, the applicant should use the NIH appropriation language salary cap and the NIH policy for graduate student compensation in developing the budget request.

For Consortium/Contractual costs, provide an estimate of total costs (direct plus facilities and administrative) for each year, each rounded to the nearest $1,000. List the individuals/organizations with whom consortium or contractual arrangements have been made, the percent effort of key personnel, and the role on the project. Indicate whether the collaborating institution is foreign or domestic. The total cost for a consortium/contractual arrangement is included in the overall requested modular direct cost amount. Include the Letter of Intent to establish a consortium.

Provide an additional narrative budget justification for any variation in the number of modules requested.

o BIOGRAPHICAL SKETCH - The Biographical Sketch provides information used by reviewers in the assessment of each individual's qualifications for a specific role in the proposed project, as well as to evaluate the overall qualifications of the research team. A biographical sketch is required for all key personnel, following the instructions below. No more than three pages may be used for each person. A sample biographical sketch may be viewed at: http://grants.nih.gov/grants/funding/modular/modular.htm

- Complete the educational block at the top of the form page;
- List position(s) and any honors;
- Provide information, including overall goals and responsibilities, on research projects ongoing or completed during the last three years.
- List selected peer-reviewed publications, with full citations.

o CHECKLIST - This page should be completed and submitted with the application. If the F&A rate agreement has been established, indicate the type of agreement and the date. All appropriate exclusions must be applied in the calculation of the F&A costs for the initial budget period and all future budget years.

o The applicant should provide the name and phone number of the individual to contact concerning fiscal and administrative issues if additional information is necessary following the initial review.

The title and number of the program announcement must be typed on line 2 of the face page of the application form and the YES box must be marked.

Application kits are available at most institutional offices of sponsored research and may be obtained from the Division of Extramural Outreach and Information Resources, National Institutes of Health, 6701 Rockledge Drive, MSC 7910, Bethesda, MD 20892-7910, telephone 301/435-0714, email: GrantsInfo@nih.gov.

Applicants planning to submit an investigator-initiated, new (type 1), competing continuation (type 2), competing supplement, or any amended/revised version of the preceding grant application types requesting $500,000 or more in direct costs for any year are advised that he or she must contact the Institute or Center (IC) program staff before submitting the application, i.e, as plans for the study are being developed. Furthermore, the application must obtain agreement from the IC staff that the IC will accept the application for consideration for award. Finally, the applicant must identify, in a cover letter sent with the application, the staff member and Institute or Center who agreed to accept assignment of the application. This policy requires an applicant to obtain agreement for acceptance of both any such application and any such subsequent amendment. Refer to the NIH Guide for Grants and Contracts, March 20, 1998 at http://grants.nih.gov/grants/guide/notice-files/not98-030.html

Submit a signed, typewritten original of the application, including the Checklist, and five signed photocopies in one package to:

CENTER FOR SCIENTIFIC REVIEW
NATIONAL INSTITUTES OF HEALTH
6701 ROCKLEDGE DRIVE, ROOM 1040, MSC 7710
BETHESDA, MD 20892-7710
BETHESDA, MD 20817 (for express/courier service)

REVIEW CONSIDERATIONS

Applications will be assigned on the basis of established PHS referral guidelines. Applications will be evaluated for scientific and technical merit by an appropriate scientific review group convened in accordance with the standard NIH peer review procedures. As part of the initial merit review, all applications will receive a written critique and undergo a process in which only those applications deemed to have the highest scientific merit, generally the top half of applications under review, will be discussed, assigned a priority score, and receive a second level review by the appropriate national advisory council or board.

Review Criteria

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. In the written comments reviewers will be asked to discuss the following aspects of the application in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals. Each of these criteria will be addressed and considered in assigning the overall score, weighting them as appropriate for each application. Note that the application does not need to be strong in all categories to be judged likely to have major scientific impact and thus deserve a high priority score. For example, an investigator may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

(1) Significance: Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge be advanced? What will be the effect of these studies on the concepts or methods that drive this field?

(2) Approach: Are the conceptual framework, design, methods, and analyses adequately developed, well-integrated, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics?

(3) Innovation: Does the project employ novel concepts, approaches or method? Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies?

(4) Investigator: Is the investigator appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers (if any)?

(5) Environment: Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support?

In addition to the above criteria, in accordance with NIH policy, all applications will also be reviewed with respect to the following:

o The adequacy of plans to include both genders, minorities and their subgroups, and children as appropriate for the scientific goals of the research. Plans for the recruitment and retention of subjects will also be evaluated.

o The reasonableness of the proposed budget and duration in relation to the proposed research.

o The adequacy of the proposed protection for humans, animals or the environment, to the extent they may be adversely affected by the project proposed in the application.

The initial review group will also examine the provisions for the protection of human subjects and the safety of the research environment.

AWARD CRITERIA

Applications will compete for available funds with all other recommended applications. The following will be considered in making funding decisions: Quality of the proposed project as determined by peer review, availability of funds, and program priority. Applications that are responsive to Program Announcements are candidates for discretionary funding. Additional information regarding NIAMS funding policy regarding these applications can be located at: http://www.nih.gov/niams/grants/payline2.htm

INQUIRIES

Inquiries are encouraged. The opportunity to clarify any issues or questions from potential applicants is welcome.

Direct inquiries regarding programmatic issues to:

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FAX: 301-480-4543
Email: jp149d@nih.gov

Ralph M. Nitkin, PhD
Biological Sciences and Career Development Program
National Center for Medical and Rehabilitation Research
National Institute of Child Health and Human Development
Executive Building, Room 2A03
6100 Executive Blvd., MSC 7510
Bethesda, MD 20892-7510
Telephone: 301-402-2242
FAX: 301-402-0832
Email: rn21e@nih.gov

Direct inquiries regarding fiscal matters to:

Sally A. Nichols
Grants Management Office
National Institute of Arthritis and Musculoskeletal and Skin Diseases
Natcher Building (45), Room 5AS-49F
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Mary Ellen Colvin
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AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance No. 93.846. Awards are made under authorization of the Public Health Service Act, Title IV, Part A (Public Law 78-410, as amended by Public Law 99-158, 42 USC 241 and 285) and administered under PHS grants policies and Federal Regulations 42 CFR 52 and 45 CFR Part 74. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

The PHS strongly encourages all grant and contract recipients to provide a smoke-free workplace and promote the non-use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, and portion of a facility) in which regular or routine education, library, day care, health care or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

Return to Volume Index
Return to NIH Guide Main Index